touchEXPERT BRIEFING

Recent updates in the field of Alzheimer's disease

GM-43471, PP-AD-IT-0040
Date of preparation: December 2023

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Online Activity Details

This resource has been downloaded from a touchEXPERT BRIEFING, hosted on touchNEUROLOGY. The full activity, which includes video resources, can be accessed at:

https://touchneurology.com/alzheimers-disease-dementia/learning-zone/recent-updates-in-the-field-of-alzheimers-disease

Learning Objectives

After watching the touchEXPERT BRIEFING activity, you should be able to:

- ✓ Understand recent progress in understanding the pathophysiology of AD including the contribution of LATE-NC co-morbidity, the role of microglia, change in wake promoting neurons and the role of GnRH
- ✓ Describe best practice approaches to the diagnosis of AD and the importance, particularly for patients, of a timely and accurate diagnosis
- ✓ Discuss the current and potential future utility of plasma and CSF biomarkers in the clinical diagnosis and prognosis of AD

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Disclosures

Prof. Dr Frank Jessen

Fees for advice and presentations (2019–2023) from Abbie, AC Immune, Biogen, Danone/Nutricia, Eisai, Eli Lilly, GE Healthcare, Grifols, Janssen and Roche; Funding from BMBF, BZGA, DFG, DZNE, Eranet Neuron, Horizon 2020, IMI, IHI, Innovationfonds (GBA) and JPND; Membership of German Association of Psychiatry (DGPPN, member of the board), German Association of Biological Psychiatry (DGBP), German Association of Geriatrics (DGGPP), German Memory Clinic Network (DNG, Chair), European Alzheimer's disease Consortium (EADC, Chair); Scientific advisory board member for German Alzheimer Association, Hirnliga Alzheimer Europe

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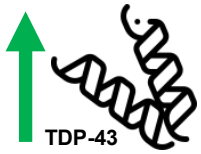
Speaker fees and/or research grants from, and has been a member of advisory boards for Eisai and Shionogi; Speaker fees from and has been a member of advisory boards for Janssen Pharmaceuticals, Chugai-Roche, and Merck Sharp & Dohme; Speaker fees and research grants from Otsuka Pharmaceutical Co Ltd, Daiichi Sankyo Company Ltd, One Pharmaceutical Co Ltd; speaker fees from Kyowa Kirin Co Ltd, UCB Japan, and Eli Lilly; Research grants from AbbVie, Dainippon Sumitomo, the Japan Agency for Medical Research and Development, and the Japan Society for the Promotion of Science.

Dr Benoît Delatour

Speaker fees from Eli Lilly

Recent updates in the pathophysiology of AD

The contribution of LATE co-morbidity to AD



LATE-NC

Characterized by the abnormal accumulation of TDP-43 and an amnestic dementia syndrome,[1, 2] and is a comorbidity in >50% of AD cases[3,4]

LATE-NC association with AD

LATE-NC in AD lowers the threshold for developing dementia, worsens cognitive decline and is associated with other neuropathological changes in the brain, such as hippocampus sclerosis[5,6]

Tome et al, demonstrated: Impact of LATE-NC on AD[4]

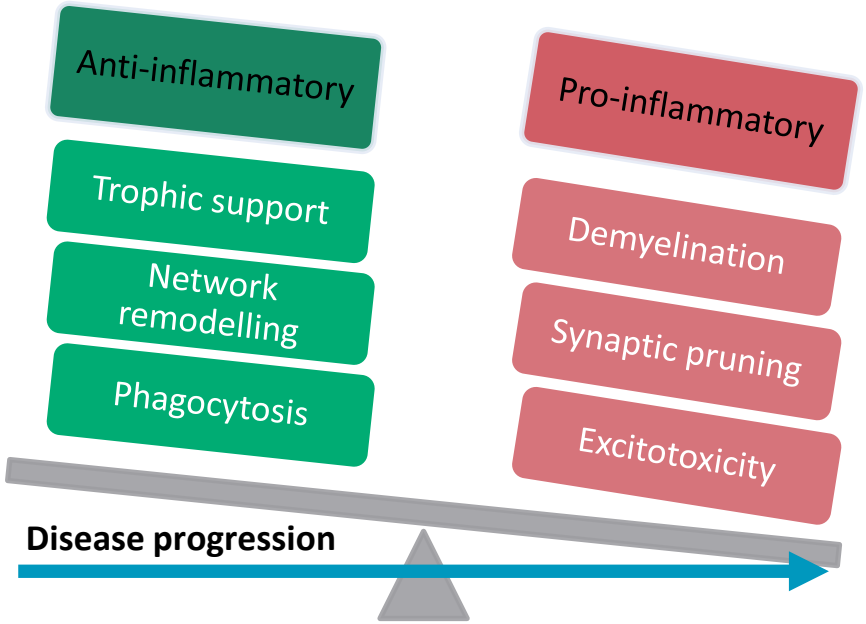
Mice: inoculation with AD brain homogenates from humans with AD plus LATE-NC increased P-tau seeding severity versus patients with AD without LATE-NC

Humans: Patients with AD plus LATE-NC have increased hippocampal tau pathology and neuronal loss vs controls

1. Meneses A, et al. *Molecular Neurodegeneration*. 2021;16(1):84; 2. Nelson PT, et al. *Brain.* 2019;142(6):1503-27; 3. Tomé SO, et al. *Brain Pathol.* 2023: e13213; 4. Tome SO, et al. *Alzheimer's Dement*. 2023; 19(Suppl. 12): e073996; 5. Josephs KA, et al. *Ann Neurol* 2015;78(5):697-709; 6. Wang SJ, et al. *Acta Neuropathol.* 2022;144(1):45-57.

AD, Alzheimer's disease; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathological changes; P, phosphorylated.

The role of microglia activation in AD



Early in AD, activated microglia positively affect pathology, but with sustained activation, release inflammatory factors, which may exacerbate tau pathology and promote AD progression[1]

1. Leng F, Edison P. *Nat Rev Neurol.* 2021;17(3):157-72.
AD, Alzheimer's disease.

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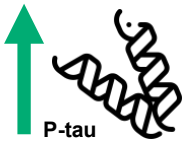
Tracking AD progression via the retina

Hart de Ruyter et al, demonstrated: Tau pathology and microglia activation is localized in the retina[1,2]



Increased levels of P-tau in the retinas of patients with AD and primary tauopathies versus controls[2]

Retinal p-tau levels and microglia correlated with Braak stages for neurofibrillary tangles[1]

P-tau levels correlate with retinal microglia counts, suggesting a pro-inflammatory environment in the presence of P-tau accumulation[2]

1. Hart de Ruyter FJ, et al. *Acta Neuropathol* 2023;145(2):197-218; 2. Hart de Ruyter FJ, et al. *Alzheimer's Dement.* 2023; 19(Suppl. 12): e076661.
AD, Alzheimer's disease; P, phosphorylated.

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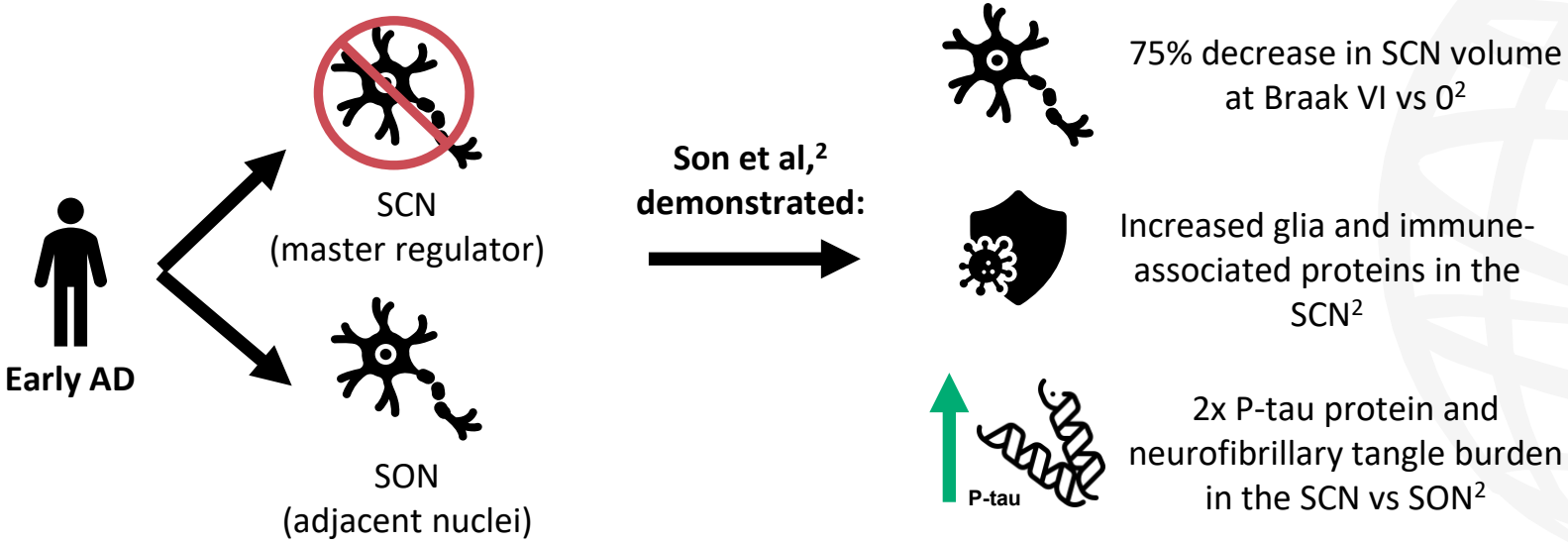
Sleep disturbances in AD

Disrupted sleep is a common feature of early AD and primary tauopathies with no amyloid accumulation[1]



The SCN in AD is differentially affected by tau toxicity compared with neighbouring nuclei

1.. Lew CH, et al. *Sleep Med Rev*. 2021;60:101541; 2. Son G, et al. *Alzheimer's Dement.* 2023; 19(Suppl. 12): e074494.
AD, Alzheimer's disease; P, phosphorylated; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus.

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Role of the GnRH in AD

Down's syndrome is characterized by amyloid deposits, neurofibrillary tangles, and clinical dementia in most patients by approximately 60 years of age[1,2]

Prevot et al, demonstrated:

Mouse model of trisomy 21[3]
Cognitive and olfactory symptoms are related to a post-pubertal decrease in GnRH expression in the hypothalamus and extra hypothalamic areas

Restoring physiological GnRH levels[3]
Rescued olfactory and memory function in mouse models of AD and trisomy 21

People with Down's syndrome[3]
In a pilot study, pulsatile GnRH therapy for six months improved cognition and stimulated brain functional connectivity

1. Head E, et al. *Curr Alzheimer Res*. 2016;13(1):18-29; 2. Lott IT, et al. *Nat Rev Neurol.* 2019;15(3):135-47; 3. Prevot V, et al. *Alzheimer's Dement*. 2023; 19(Suppl. 12): e074955.
AD, Alzheimer's disease; GnRH, gonadotropin-releasing hormone.

The role of biomarkers in diagnosis, staging, and characterisation of AD

Optimal patient pathway with suspected early AD

The first potential symptoms of cognitive decline are assessed by the PCP

A short cognitive test, sensitive to subtle impairment is performed to determine whether there is impairment

Other potential sources of cognitive impairment e.g. thyroid dysfunction and medication side effects are excluded

Specialist referral for extended neuropsychological assessment to determine the level of impairment and function in daily living

If presence of mild cognitive impairment/mild dementia is confirmed, brain imaging is used e.g. to determine pattern of atrophy or vascular lesions, and AD biomarker assessment is performed to establish etiology

At a disclosure meeting, the patient is informed of the diagnosis and the next disease management steps are discussed

1. Porsteinsson AP, et al. *J Prev Alz Dis*. 2021;3(8):371-386; 2. Iliffe S. et al. *Int J Geriatr Psychiatry.* 2009;24:895–901.
AD, Alzheimer's disease; PCP, primary care physician.

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Biomarkers for the diagnosis and staging of AD

Aβ	Tau
Aβ42 and Aβ42/40 ratio[1] Aβ42/40 ratio correlates with the cerebral amyloid. This has been shown in studies against amyloid PET[1] and post-mortem confirmation[2]	**P-tau 181 and 217, and total tau** P-tau 181 correlates with the aggregated P-tau and the neurofibrillary tangles in the brain;[1] total tau is non-specific, indicating general neuronal damage[2]
Amyloid PET Detects amyloid plaques in the brain and is highly validated by a post-mortem analysis[2]	**tau PET** Detects tau neurofibrillary tangles in the brain and has been validated in post-mortem studies[2]

Further biomarkers are in development including CSF NFl and BBM biomarkers,[2]
although currently the NIA-AA propose using Aβ and tau-based biomarkers for both diagnosis and staging[3]

1. Luebke M, et al. *Biomark Neuropsychiatry*. 2023;8:100062; 2. Andersen E, et al. *Biomark Neuropsychiatry*. 2021;5:100041;
3. Jack CR, et al. *Alzheimers Dement.* 2018;14(4):535-562.
Aβ, amyloid beta; BBM, blood-based biomarkers; P, phosphorylated; CSF, cerebrospinal fluid; NFl, neurofilament light chain; PET, positron emission tomography.

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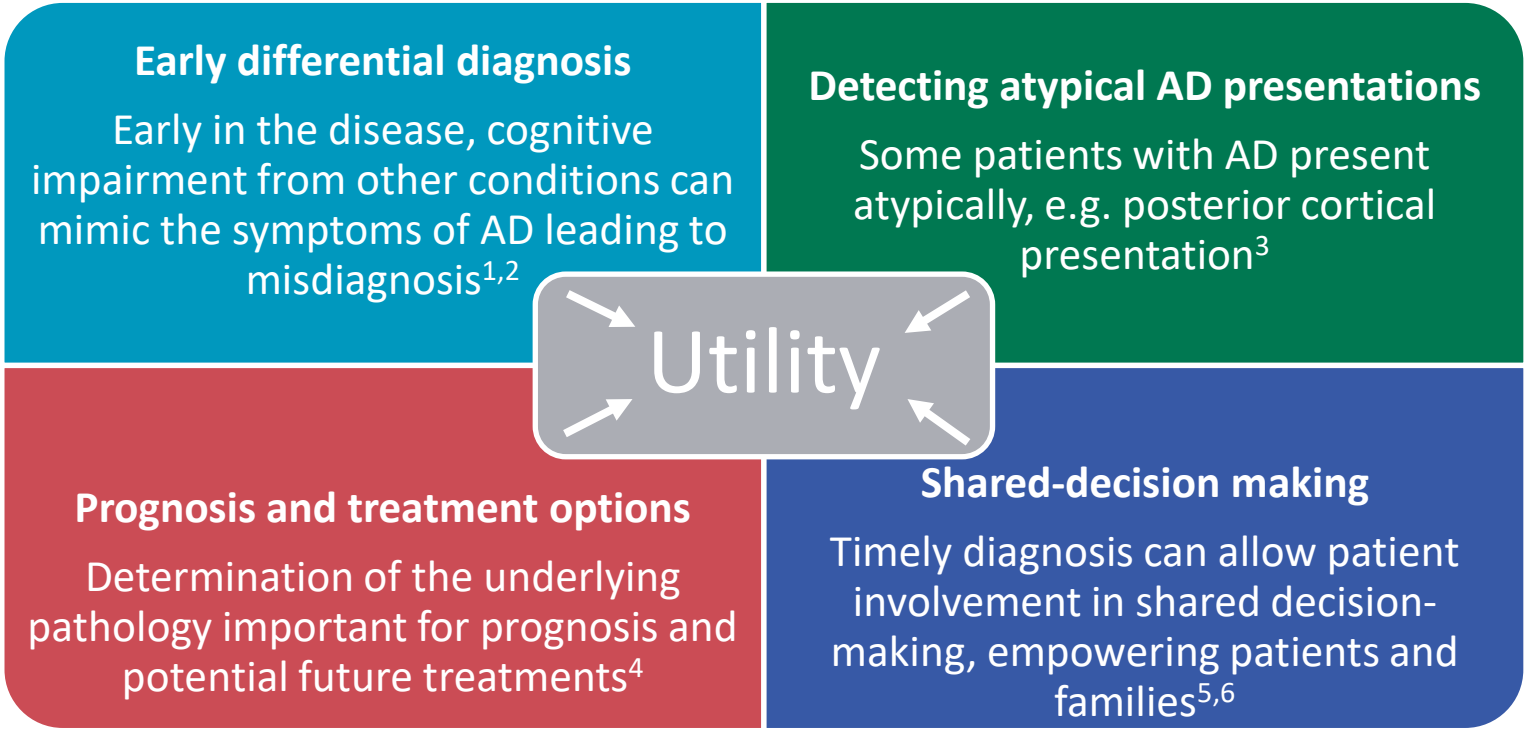
Utility of biomarkers in AD

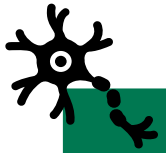


1. Luebke M, et al. *Biomark Neuropsychiatry.* 2023;8:100062. 2. Paraskevaidi M, et al. *PNAS* 2017: 114 (38);E7929-E7938; 3. Graff-Radford J, et al. *Lancet Neurol.* 2021;20(3):222-234; 4. Dubois B, et al. *Alzheimers Res Ther.* 2023;15(1):175; 5. Dubois, B, et al. *J Alzheimers Dis.* 2016;49(3):617-31; 6. Liss JL, et al. *J Intern Med.* 2021;290(2):310-334.
AD, Alzheimer's disease.

Advantages and limitations of AD biomarkers[1,2]

PET

- Provides in vivo localization of amyloid or tau pathology[2]
- Expensive[1,2]
- Radioactive[1]
- Access limitations[2]



CSF

- Can measure multiple biomarkers
- Accessible from cost and training perspectives[1,2]
- Does not indicate brain location of the AD pathology
- Limited by the need to perform a lumbar puncure[3]

BBM

- Easy to collect
- Can assess multiple biomarkers and can be repeated
- Does not allow localization of brain pathology
- Requires additional validation for accuracy and thresholds need to be globally standardized[1]

1. Andersen E, et al. *Biomark Neuropsychiatry*. 2021;5:100041; 2. Luebke M, et al. *Biomark Neuropsychiatry.* 2023;8:100062; 3. Henriksen MJV, et al. *J Gen Intern Med.* 2018;33(2):148-154.

AD, Alzheimer's disease; BBM, blood-based biomarkers; CSF, cerebrospinal fluid; PET, positron emission tomography.

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Steps for implementing BBMs

1. Establish appropriate use and threshold criteria for BBM[1]

2. Improve infrastructure for analyzing and reporting BBM values to prevent long-waiting lists for screening[2]

3. Provide physicians education on the selection of appropriate biomarkers for testing, and how to interpret test results in symptomatic patients

1. Hansson O, et al. *Alzheimers Dement.* 2022;18(12):2669-86; 2. Hlavka JP, et al. Santa Monica, CA: RAND Corporation; 2018.
BBM, blood-based biomarkers.

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Ensuring consensus guidelines are up to date

Challenge: ensure that consensus guidelines remain relevant when rapid innovation is taking place

Leitthema

Nervenarzt 2023 · 94:609–613
https://doi.org/10.1007/s00115-023-01492-6
Angenommen: 12. April 2023
Online publiziert: 26. Mai 2023

Die S3-Leitlinien *Demenzen*

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Potential solution: use a digital living guideline as in Germany,[1]
allowing for the continuous adoption of individual recommendations as new innovations are validated

1. Jessen F. et al. *Nervenarzt*. 2023;94(7):609-613.
AD, Alzheimer's disease.

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Summary

Summary

1. New understanding of AD pathophysiology may lead to novel biomarkers and disease treatment strategies
2. Both PET and CSF-based biomarkers are available for AD diagnosis and staging, each with their own pros and cons
3. BBMs require additional validation for accuracy and clinical thresholds but their accessibility may facilitate a timely and accurate AD diagnosis

This activity is sponsored

This activity has been sponsored by Eli Lilly.

Eli Lilly provided financial support and has had input into the selection of the faculty and the detailed project scope. This activity is provided by Touch Medical Communications (TMC) for touchNEUROLOGY.

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